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18-Methoxycoronaridine (18-MC) and Ibogaine

Comparison of Antiaddictive Efficacy, Toxicity, and Mechanisms of Action

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ABSTRACT: 18-MC, a novel *iboga* alkaloid congener, is being developed as a potential treatment for multiple forms of drug abuse. Like ibogaine (40 mg/kg), 18-MC (40 mg/kg) decreases the intravenous self-administration of morphine and cocaine and the oral self-administration of ethanol and nicotine in rats; unlike ibogaine, 18-MC does not affect responding for a nondrug reinforcer (water). Both ibogaine and 18-MC ameliorate opioid withdrawal signs. Both ibogaine and 18-MC decrease extracellular levels of dopamine in the nucleus accumbens, but only ibogaine increases extracellular levels of serotonin in the nucleus accumbens. Both ibogaine and 18-MC block morphine-induced and nicotine-induced dopamine release in the nucleus accumbens; only ibogaine enhances cocaine-induced increases in accumbal dopamine. Both ibogaine and 18-MC enhance the locomotor and/or stereotypic effects of stimulants. Ibogaine attenuates, but 18-MC potentiates, the acute locomotor effects of morphine; both compounds attenuate morphine-induced locomotion in morphine-experienced rats. Ibogaine produces whole body tremors and, at high doses (≥ 100 mg/kg), cerebellar damage; 18-MC does not produce these effects. Ibogaine, but not 18-MC, decreases heart rate at high doses. While 18-MC and ibogaine have similar affinities for kappa opioid and possibly nicotinic receptors, 18-MC has much lower affinities than ibogaine for NMDA and sigma-2 receptors, sodium channels, and the 5-HT transporter. Both 18-MC and ibogaine are sequestered in fat and, like ibogaine, 18-MC probably has an active metabolite. The data suggest that 18-MC has a narrower spectrum of actions and will have a substantially greater therapeutic index than ibogaine.

INTRODUCTION

18-Methoxycoronaridine (18-MC) is a synthetic *iboga* alkaloid congener, derived from the putative antiaddictive drug, ibogaine (FIGURE 1), a naturally occurring indole alkaloid found in the root bark of the West African shrub, *Tabernanthe iboga*. In five United States patents, issued between 1985 and 1992 (numbers 4,499,096; 4,587,243; 4,857,523; 5,026,697; 5,124,994), ibogaine has been claimed to interrupt

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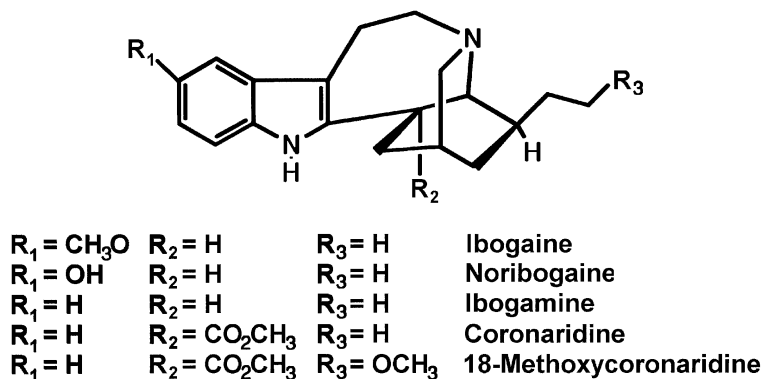


FIGURE 1. Chemical structures of ibogaine, 18-methoxycoronaridine, and related compounds.

the “physiological and psychological aspects” of addiction to opioids (heroin), stimulants (cocaine and amphetamine), alcohol, and cigarettes (nicotine) and of poly-drug abuse. These patents claim that single oral treatments with ibogaine (6–19 mg/kg) can abolish drug craving and withdrawal symptoms for up to 6 months and that repeated treatments (a series of four oral administrations) are effective at blocking craving and withdrawal for up to 3 years in chronic drug users. Since the issue of these patents, several animal studies have provided some experimental support for ibogaine’s ability to attenuate the self-administration of a variety of drugs. Both single and repeated doses of ibogaine can reduce the self-administration of morphine,^{1,2} cocaine,^{2–4} alcohol,⁵ and nicotine⁶ in rodents. Consistent with human reports,⁷ these antiaddictive effects were reported to last for at least 24 h, and up to several weeks in some rats,¹ well beyond the presence of the drug or its active metabolite, noribogaine, in the brain.^{8,9} In addition, the claim that ibogaine also reduces the symptoms of narcotic withdrawal is substantiated by some ibogaine researchers using animal models of opioid withdrawal (naloxone- or naltrexone-precipitated withdrawal in animals physically dependent on morphine). In general, ibogaine was efficacious at reducing some, if not most, signs of opioid withdrawal in rats,^{10,11} monkeys,¹² and mice.¹³

Besides having both hallucinogenic and stimulant properties (factors that ultimately led to the classification of ibogaine as a Schedule 1 substance by the FDA in 1970), ibogaine induces whole body tremors in rats. This effect appears to be due to an activation of an olivocerebellar pathway by ibogaine when the drug is administered in moderate doses (20–40 mg/kg) (cf. reference 14); tremors are reduced at higher ibogaine doses (≥ 100 mg/kg), presumably due to an overstimulation of cerebellar Purkinje cells,^{14–16} which produces damage to the cerebellar vermis. In addition, ibogaine induces a pronounced bradycardia (decrease in heart rate) in rodents,¹⁷ a side effect that arguably may be of greater clinical significance.

The undesirable side effects associated with ibogaine led to attempts by our colleagues, M. Kuehne and U. Bandarage (University of Vermont), to synthesize safer and equally efficacious *iboga* alkaloid derivatives. Of the compounds assessed for

antiaddictive efficacy in rat models of drug self-administration, two nontremorigenic *iboga* alkaloids, *R*-ibogamine and *R*-coronaridine, and several synthetic analogues of ibogamine and coronaridine mimicked ibogaine's effects on morphine and cocaine self-administration.² These studies demonstrated that the ability of *iboga* compounds to attenuate drug self-administration can be dissociated from its tremorigenic activity. However, the *iboga* compounds initially synthesized also reduced responding for a nondrug reinforcer (water), as well as responding for drugs, during the first 1–2 hours after their administration. In contrast, 18-MC appeared to have a different profile of activity: this synthetic *iboga* congener alkaloid decreased both morphine and cocaine self-administration, without producing any detectable effects on motor behavior, the cerebellum, heart rate, or responding for water. Further assessment of the potential antiaddictive efficacy of 18-MC demonstrated that this compound also reduced the intake of alcohol and nicotine and attenuated some signs of acute morphine withdrawal in rats. This paper will review our current understanding of the *in vivo* and *in vitro* pharmacological actions of 18-MC and compare them with those of the prototypical *iboga* agent, ibogaine.

BEHAVIORAL PHARMACOLOGY

Drug Self-Administration Studies

The antiaddictive efficacies of both ibogaine and 18-MC have been assessed using a rat model of drug addiction. For studies of cocaine and morphine, female rats (250 ± 20 g) were first trained to self-administer drug intravenously (iv) according to procedures described previously.^{1,2,18} Briefly, following sessions during which the bar-press response was shaped by training rats to bar-press for water, rats were trained to self-administer morphine (0.04 mg/kg/infusion) or cocaine (0.4 mg/kg/infusion) during daily 1-hour test sessions. During these sessions, each bar-press resulted in an iv infusion of either a 10 μ l (morphine) or 50 μ l (cocaine) drug solution (0.01 mg of morphine sulfate or 0.1 mg cocaine hydrochloride) in 0.1 (morphine) or 0.5 (cocaine) seconds. To assess the drug specificity of the effects of ibogaine and 18-MC, control rats were trained to bar-press for water on a comparable conditioned reinforcement schedule. For studies of nicotine self-administration, rats were trained to orally self-administer (–)-nicotine (4 μ g/ml of the hydrogen bitartrate salt) in a two-lever operant paradigm in which pressing of the nicotine lever resulted in delivery of the nicotine solution into a drinking cup, whereas pressing of the alternate lever resulted in water delivery.⁶ The effects of ibogaine and 18-MC on alcohol intake were determined in male, alcohol-preferring rats in a two-bottle choice paradigm in which rats were allowed to drink for 24 hours from one bottle containing a 10% (v/v) ethanol solution or another bottle containing water.^{5,19}

The acute intraperitoneal (ip) administration of either ibogaine or 18-MC, 15 min prior to testing, dose-dependently decreased the self-administration of morphine,^{1,18} cocaine,^{2,18} nicotine,⁶ and alcohol^{5,19} in rats. As depicted in FIGURE 2, ibogaine and 18-MC were equipotent in attenuating cocaine (top, left) and morphine (top, right) self-administration. Similarly, higher doses of both ibogaine and 18-MC decreased nicotine intake (bottom, left), but only the effect of 18-MC was selective for nicotine; ibogaine decreased water intake at all doses tested⁶ (bottom, right). Studies of

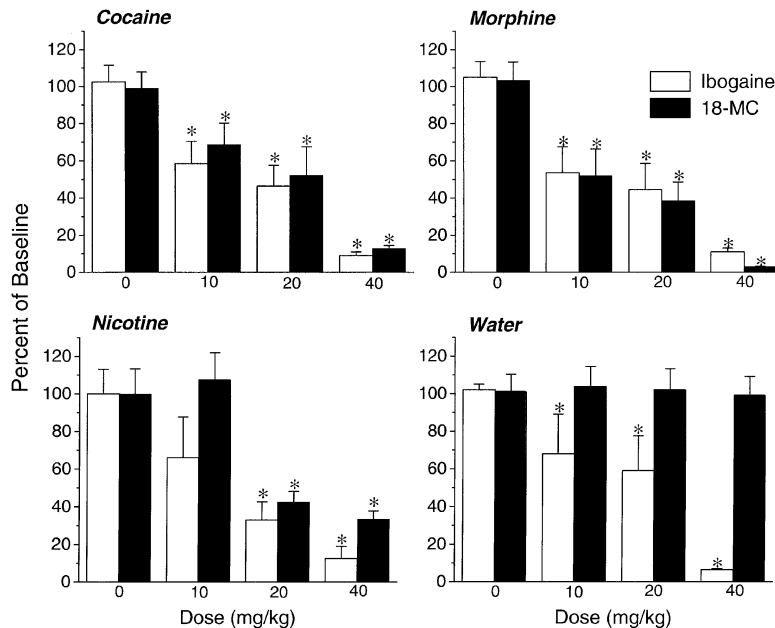


FIGURE 2. Comparison of the dose-response effects of intraperitoneally administered ibogaine and 18-MC (40 mg/kg, ip, 30 min earlier) on the self-administration of cocaine (top, left), morphine (top, right), nicotine (bottom, left), and water (bottom, right). Each bar represents the mean ($\pm$ SEM) of at least 6 rats. Asterisks indicate significant differences ($p < 0.05$) from vehicle (0 mg/kg).

alcohol consumption demonstrated that both ibogaine and 18-MC (10–40 mg/kg, ip) reduced alcohol intake; however, ibogaine produced nonspecific effects on food and/or water intake at all doses tested (10, 20 and 40 mg/kg, ip), whereas nonspecific effects were only apparent at the highest 18-MC dose tested (40 mg/kg, ip).^{5,19} Thus, the acute effects of 18-MC on drug self-administration are more specific than those of its parent compound, ibogaine.

The effects of ibogaine and 18-MC on drug self-administration are protracted; pretreatment with either 40 mg/kg ibogaine or 18-MC decreased morphine and cocaine self-administration for at least 24 hours (FIGURE 3).^{1,2,18} Similar effects on morphine self-administration were also observed following oral pretreatment, via gavage, with 18-MC.²⁰ Although the acute effects of ibogaine on drug self-administration can be attributed to the induction of whole body tremors, the aftereffects of ibogaine on drug self-administration occur at times when the drug is eliminated from the body and tremors are absent.¹ The effects of 18-MC on drug self-administration also persist long after 18-MC itself is eliminated.^{18,20}

Consistent with human anecdotal reports, the antiaddictive efficacies of both ibogaine and 18-MC seem to increase with repeated treatment. Weekly or biweekly injections of ibogaine (3–4 injections of 40 mg/kg, ip) can increasingly suppress morphine intake for up to a week in some rats¹ and repeated daily administration of

TABLE 1. Comparison of the dose-response effects of ibogaine and 18-MC on several signs of acute naltrexone-precipitated withdrawal in morphine-dependent rats

Parameter	Ibogaine (mg/kg)				18-MC (mg/kg)			
	0	10	20	30	0	10	20	40
Weight loss (%)	100.0 ± 5.0	81.3 ± 7.5	90.0 ± 5.0	70.0 ± 8.0	100.0 ± 14.9	70.9 ± 10.6	69.5 ± 5.0	53.2 ± 5.7*
Wet dog shakes	100.0 ± 15.0	97.5 ± 15.0	57.5 ± 8.5*	47.5 ± 2.5*	100.0 ± 22.2	125.3 ± 39.1	3.1 ± 35.8*	8.1 ± 66.0
Flinching	100.0 ± 26.0	76.0 ± 17.0	40.0 ± 15.0	72.5 ± 20.0	100.0 ± 36.5	48.9 ± 23.8	35.7 ± 9.5	63.5 ± 17.5
Grooming	100.0 ± 17.5	35.0 ± 5.5*	12.5 ± 4.5*	2.5 ± 0.3*	100.0 ± 10.6	190.6 ± 51.8	56.5 ± 21.1	103.5 ± 29.4
Teeth chattering	100.0 ± 22.5	27.5 ± 12.5	5.0 ± 1.5*	2.5 ± 2.0*	100.0 ± 14.0	62.0 ± 15.1	53.9 ± 12.1*	28.4 ± 11.8*
Burying	100.0 ± 20.0	80.0 ± 17.5	77.5 ± 16.0	102.5 ± 21.0	100.0 ± 33.3	155.1 ± 34.8	46.4 ± 4.4	5.8 ± 2.9*
Diarrhea	100.0 ± 21.0	34.0 ± 11.0	20.0 ± 9.0*	7.5 ± 5.0*	100.0 ± 20.0	50.0 ± 15.0	75.0 ± 15.0	40.0 ± 10.0*

NOTE: Values are means (±SEM) of at least 6 rats (**p* < 0.05).

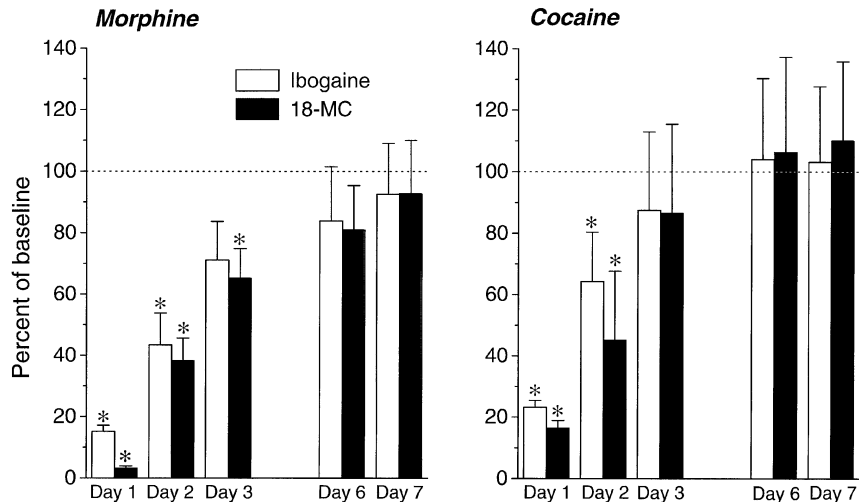


FIGURE 3. Comparison of the aftereffects of pretreatment (30 min prior to day 1 testing) with either ibogaine or 18-MC (40 mg/kg, ip) on the self-administration of morphine (left) and cocaine (right). Each bar represents the mean percent of baseline levels of responding ($\pm$ SEM) of at least 6 rats. Dotted lines represent the mean baseline level of responding. Asterisks indicate significant differences ($p < 0.05$) from baseline.

18-MC (5 injections of 20 mg/kg, po), while having little to no effect on self-administration on day 1 of treatment, decreased morphine intake by day 4.²⁰ In the case of 18-MC, repeated treatment (up to 5 days) failed to alter responding for water.²⁰ Considered together, these results indicate that the protracted effects of both acute and/or repeated ibogaine and 18-MC treatment are completely selective for drug versus nondrug reinforcers.

Acute Morphine Withdrawal

It has been claimed that ibogaine “suppresses the multiple symptoms and physical discomfort of narcotic withdrawal” (ENDABUSE™ product information). As such, the effects of ibogaine¹¹ and 18-MC²¹ pretreatment (40 mg/kg, ip, 30 min earlier) were assessed in an animal model of morphine withdrawal, in which signs of withdrawal were induced in morphine-dependent rats by the acute administration of a μ opioid receptor antagonist (naltrexone). TABLE 1 summarizes these findings. In brief, both ibogaine and 18-MC reduced the intensity of several signs of morphine withdrawal in rats; however, their effects were not identical. Thus, ibogaine produced dose-dependent decreases in wet dog shakes, grooming, teeth chattering, and diarrhea,²⁶ whereas 18-MC decreased weight loss, wet dog shakes, teeth chattering, burying, and diarrhea.⁶⁴ Although both ibogaine and 18-MC are effective at reducing some signs of morphine withdrawal, the data suggest that they may produce these effects via different mechanisms.

Locomotor and Stereotypy Studies

Stimulants (e.g., amphetamine and cocaine) and opioids (e.g., morphine) can induce pronounced alterations of motor behavior in rats, and the chronic administration of such addictive substances can lead to progressive increases in the motor behavior of these drugs (e.g., references 22 and 23). Termed "sensitization", this phenomenon has been theoretically implicated in the development of drug addiction^{24,25} and drug-induced psychosis.^{22,26,27} As such, effects of ibogaine and 18-MC on drug-induced motor behavior, and on the sensitization of this behavior, were assessed in rats treated with morphine, cocaine, or methamphetamine.

Initial work demonstrated that a "therapeutically effective" dose (i.e., 40 mg/kg, ip) of either ibogaine or 18-MC, when administered either 1 or 19 hours prior to testing, did not significantly alter the spontaneous locomotor activity of rats.^{20,28–30} In contrast, both ibogaine and 18-MC (40 mg/kg, ip, 19 hours earlier) did alter the acute locomotor-activating effects of stimulant (cocaine and amphetamines) and opioid (morphine) drugs. With respect to stimulant-induced locomotion, both compounds augmented the expression of locomotor behavior in response to cocaine^{28,30–32} (FIGURE 4) and amphetamines.^{33,34} In the case of cocaine, ibogaine and 18-MC both

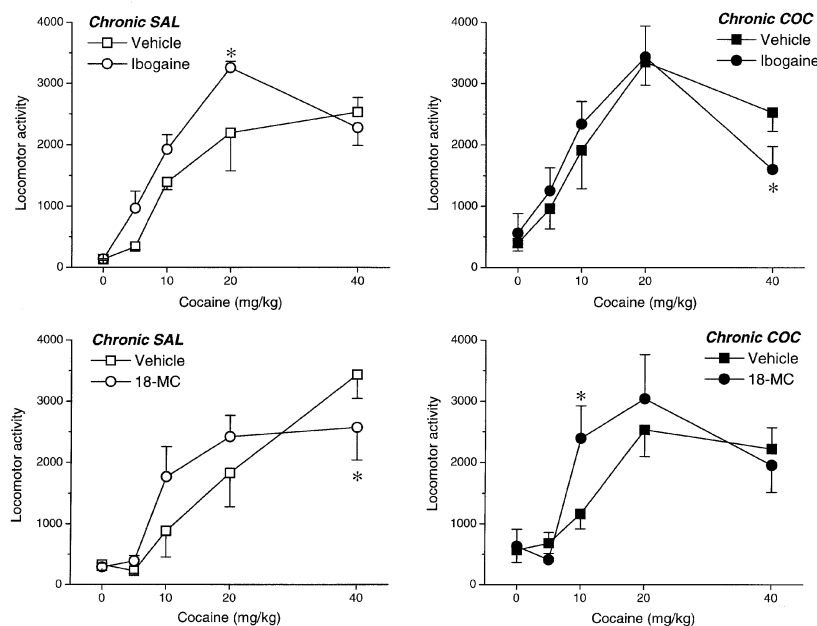


FIGURE 4. Comparison of the effects of ibogaine (top) and 18-MC (bottom) (40 mg/kg, ip, 19 h earlier) on the dose-response curve for cocaine-induced locomotion in rats treated chronically with either saline (left) or cocaine (5×15 mg/kg, ip; right). Each data point represents the mean ($\pm$ SEM) of at least 6 rats. ANOVA showed a significant ($p < 0.05$) pretreatment effect (top left), significant ($p < 0.05$) pretreatment $\times$ dose interactions (top right; bottom left), and a significant ($p < 0.05$) pretreatment $\times$ dose $\times$ time interaction (bottom right). Asterisks indicate significant differences ($p < 0.05$; post-hoc tests) from vehicle.

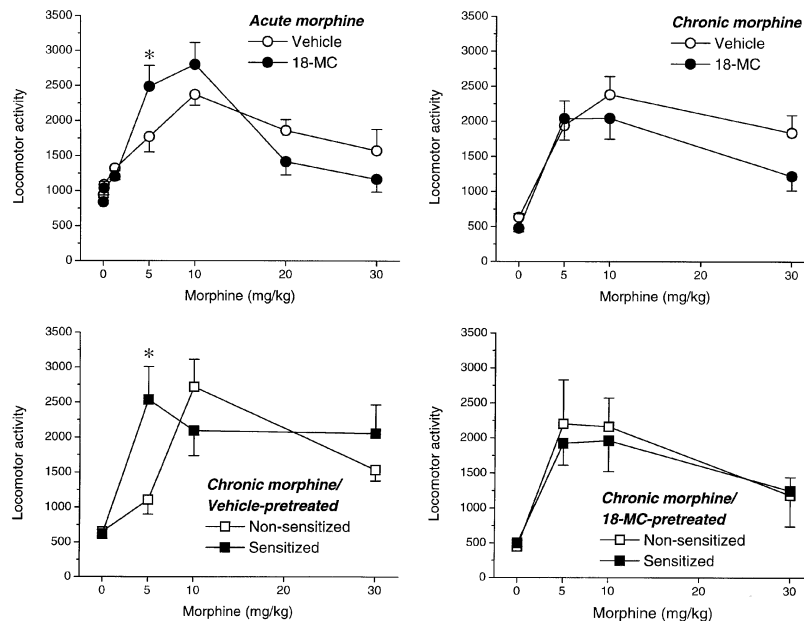


FIGURE 5. Top: The effects of 18-MC (40 mg/kg, ip, 19 h earlier) on the dose-response curve for morphine in acute (left) and chronic (right) morphine-treated rats. Bottom: Comparison of the dose-effect curves for morphine in chronic morphine-treated rats pretreated with vehicle (left) or 18-MC (right). Each data point represents the mean total locomotor activity ($\pm$ SEM) of at least 7 rats. ANOVA showed a significant ($p < 0.05$) pretreatment $\times$ dose interaction in acute morphine-treated rats (top left) and a significant ($p < 0.05$) group $\times$ dose interaction in chronic morphine/vehicle-pretreated rats (bottom left). Asterisks indicate significant differences ($p < 0.05$; post-hoc tests) from vehicle (top left) or between groups (bottom left).

shifted the dose-response curve of acute cocaine-treated animals to the left of controls,³² indicating that pretreatment with these *iboga* agents renders an animal more sensitive to cocaine's acute locomotor effects (FIGURE 4, left). In contrast, ibogaine and 18-MC had opposite effects on locomotion induced by an acute injection of morphine; ibogaine decreased morphine-induced locomotion,^{9,29,35} whereas 18-MC potentiated it, as evidenced by an 18-MC-induced shift to the left in the dose-response curve (FIGURE 5, top left).

Studies of the effects of ibogaine on the expression of motor behavior in rats repeatedly administered drugs of abuse indicated that ibogaine's effects are greater, or possibly different, than those observed for acute drug-induced behavior. Ibogaine (40 mg/kg, ip, 19 h beforehand) produced a greater attenuation of morphine-induced (5 mg/kg, ip) locomotion in rats previously (2–4 times) administered morphine (30 mg/kg, ip) compared to acutely treated rats.³⁵ In an early study, ibogaine (40 mg/kg, ip, 24 h beforehand) also attenuated the locomotor response to *d*-amphetamine (1.5 mg/kg, ip) in rats repeatedly administered *d*-amphetamine (4×1.5 mg/kg, every other day).³⁴ More recently, pretreatment with ibogaine or 18-MC (40 mg/kg, ip,

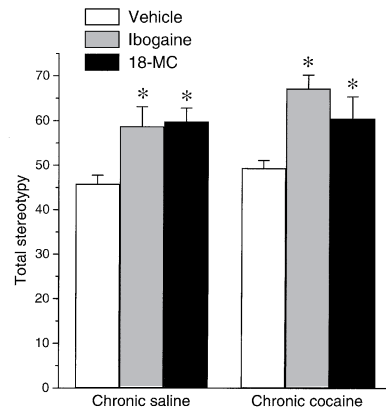


FIGURE 6. Effects of ibogaine and 18-MC (40 mg/kg, ip, 19 h earlier) on the expression of cocaine-induced (40 mg/kg, ip) stereotypy in rats treated chronically with either saline or cocaine. Each bar represents the mean total stereotypy score of 6 rats ($\pm$ SEM). Asterisks indicate significant differences ($p < 0.05$) from vehicle.

19 h earlier) was found to shift the inverted U-shaped dose-response curves for locomotion in chronic cocaine-treated rats to the left of controls such that *iboga* pretreated rats displayed augmented locomotor activation at lower cocaine doses (e.g., 5 and 10 mg/kg)^{31,32} and lower levels of locomotor activation at higher cocaine doses (e.g., 20 and 40 mg/kg) compared to control animals³² (FIGURE 4, right). The locomotor-attenuating effects of *iboga* pretreatment at higher cocaine doses can be attributed to the induction of repetitive, species-specific behaviors (*stereotypy*), which can be physically incompatible with locomotion (e.g., focused sniffing, grooming, gnawing); ibogaine and 18-MC (40 mg/kg, ip, 19 h earlier) promote the expression of high levels of cocaine-induced stereotypic behavior in both acute and chronic cocaine-treated rats, compared to controls (FIGURE 6). Virtually identical effects of ibogaine and 18-MC pretreatment were observed for methamphetamine-induced stereotypy. This latter finding may possibly account for the previously reported³⁴ attenuating effect of ibogaine on *d*-amphetamine-induced locomotion in chronic *d*-amphetamine-treated rats. Combined, these findings indicate that ibogaine and 18-MC pretreatments augment a rat's sensitivity to the behavioral-activating effects of stimulant drugs and that this increase can be above and beyond that produced by chronic stimulant administration.

With regard to morphine-induced locomotion, in contrast to ibogaine,³⁵ 18-MC failed to alter significantly the locomotor-activating effects of morphine in chronic morphine-treated rats (FIGURE 5, top, right). Interestingly, however, 18-MC (40 mg/kg, ip, 19 h earlier) blocked the expression of locomotor sensitization following chronic morphine administration. As depicted in FIGURE 5 (bottom), the dose-effect curve of control rats sensitized by chronic morphine administration was shifted to the left of control rats that did not sensitize as a result of chronic morphine experience; however, the dose-effect curves of 18-MC-pretreated sensitized and nonsensitized rats were virtually identical. Thus, whereas ibogaine produces a greater effect on morphine-induced behavior in drug-experienced animals, compared to naive animals, 18-MC masks, or possibly reverses, the alterations in behavior produced by chronic morphine experience, apparently returning the animal to its initial nonsensitized state.

POTENTIAL MECHANISMS OF ACTION

In Vivo Microdialysis Studies

Many or possibly all addictive drugs (including opioids, stimulants, ethanol, and nicotine) share an ability to enhance mesotelencephalic dopamine transmission (see references 36–38); the repeated administration of addictive drugs typically renders the mesotelencephalic dopamine systems hypersensitive, enhancing or sensitizing the dopamine response upon subsequent drug administration.^{22,23,39,40} That the chronic administration of addictive drugs produces neuroadaptations in the mesotelencephalic dopamine systems is important when one considers the wealth of evidence supporting the putative role for dopamine, particularly in the limbic targets of the mesotelencephalic system (including the nucleus accumbens), as a critical mediator of the “rewarding” or “incentive motivational” effects of drugs of abuse,^{41,42} as well as other natural reinforcers such as food, sex, avoidance, and others.⁴³ Consistent with their antiaddictive actions, ibogaine and 18-MC (40 mg/kg, ip) both produce a progressive decrease in accumbal dopamine release during the first 3 h after their administration.^{18,44} In addition, consistent with their antiaddictive effects, but not necessarily their locomotor effects, ibogaine and 18-MC (40 mg/kg, ip, 19 h earlier) affect the alterations of accumbal dopamine transmission produced by a variety of drugs of abuse. Both compounds block acute morphine-induced^{18,44} and acute nicotine-induced^{6,45} increases in extracellular levels of dopamine in the nucleus accumbens (FIGURE 7, top). Like its effects on sensitized locomotor behavior, we have recently found that 18-MC (40 mg/kg, ip, 19 h earlier) also completely abolishes the sensitized dopamine response to morphine in rats chronically administered morphine, a finding consistent with a greater attenuation of morphine-induced dopamine release by ibogaine in rats having previous exposure to morphine.⁴⁶

Distinctions between ibogaine and 18-MC have been reported with respect to some of their neurochemical effects. For one, ibogaine as well as noribogaine increase extracellular levels of serotonin in the nucleus accumbens, whereas 18-MC has no effect.⁴⁷ Second, ibogaine augments²⁸ cocaine-induced increases in extracellular levels of dopamine in the nucleus accumbens (FIGURE 7, bottom), whereas 18-MC has no effect.²⁰ These findings for 18-MC are now being extended to cocaine-sensitized animals; preliminary results indicate that 18-MC has an effect. The effects of ibogaine pretreatment on cocaine-sensitized levels of dopamine in the nucleus accumbens have not yet been assessed. Nonetheless, these microdialysis studies indicate that 18-MC and ibogaine have somewhat different mechanisms of action and that different mechanisms underlie their behavioral interactions with opioid versus stimulant drugs.

In Vitro Pharmacology

An extensive receptor screen comparing the binding affinities of 18-MC, ibogaine, and its active metabolite, noribogaine, demonstrated that the binding profiles for 18-MC are somewhat different from those of its parent compound. The results of this screen are presented in TABLE 2. Consistent with previous studies (cf. ref. 48), ibogaine and noribogaine have low micromolar affinities for the κ and μ opioid receptors, the NMDA subtype of glutamate receptor, 5-HT₃ receptors, sigma-2

TABLE 2. Interactions of (±)-18-MC, ibogaine, and noribogaine with the target sites listed below

	Ligand	Tissue	(±)-18-MC	Ibogaine	Noribogaine
Kappa opioid	[³ H]-U69593	calf cortex	5.1 ± 0.50	2.2 ± 0.10	0.61 ± 0.015
Mu opioid	[³ H]-DAGO	calf cortex	1.1 ± 0.30	2.0 ± 0.15	0.68 ± 0.016
Delta opioid	[³ H]-DPDPE	calf caudate	3.5 ± 0.05	>10	5.2 ± 0.64
Nociceptin	[³ H]-nociceptin	bovine cortex	>100	>100	>100
NMDA	[³ H]-MK801	bovine cortex	>100	3.1 ± 0.30	15 ± 2.0
D1	[³ H]-SCH23390	calf caudate	>100	>10	>10
D2	[³ H]- <i>N</i> -methyl-spiperone	calf caudate	16 ± 0.60	>10	>10
D3	[³ H]-7-OH-DPAT	calf caudate	25 ± 2.5	70 ± 1.7	>100
M1	[³ H]-pirenzepine	calf cortex	32 ± 3	16 ± 1.0	15 ± 1.0
M2	[³ H]-QBN	calf cortex	>100	31 ± 3.4	36 ± 3.7
5-HT1A	[³ H]-8-OH-DPAT	rat hippocampus	46 ± 4.9	>100	>100
5-HT1B	[³ H]-serotonin	calf caudate	>100	>100	>100
5-HT1C	[³ H]-mesulergine	calf cortex	>100	>100	>100
5-HT1D	[³ H]-serotonin	calf caudate	>10	>100	>100
5-HT2A	[³ H]-ketanserin	Gf-6 cells	40 ± 3.4	16	>100
5-HT2C	[³ H]-mesulergine	J-1 cells	>100	>10	>10
5-HT3	[³ H]-GR-65,630	NG-108 cells	3.8 ± 0.067	2.6 ± 0.23	>100
Sodium channel	[³ H]-BTX-B	Bovine cortex	6.4 ± 0.68	3.6 ± 0.35	17 ± 0.6
Sigma 1	[³ H]-(+)-pentazocine	calf caudate	>100	2.5 ± 0.6	11 ± 1.7
Sigma 2	[³ H]-DTG	calf hippocampus	13 ± 1.2	0.4 ± 0.036	19 ± 1.3
GABA B	[³ H]-GABA	calf cortex	>100	>100	>100
NE uptake	[³ H]-nisoxetine	bovine cortex	>10	>100	39 ± 1.5
5-HT uptake	[³ H]-paroxetine	bovine brain stem	>10	4.1 ± 0.83	0.57 ± 0.083

NOTE: Values are μM K_i .

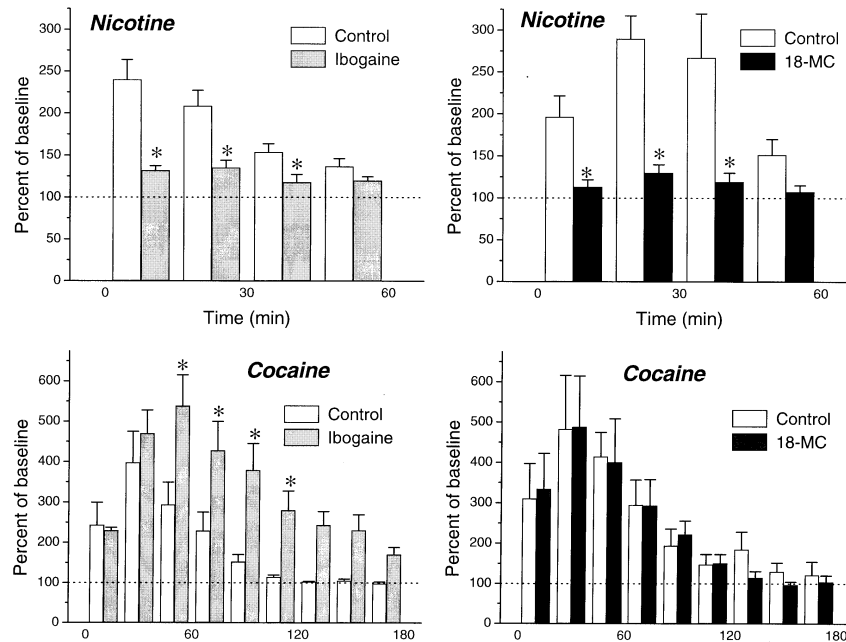


FIGURE 7. Top: Comparison of the effects of ibogaine and 18-MC (40 mg/kg, ip, 19 h earlier) on acute nicotine-induced increases in extracellular levels of dopamine in the NAC. Bottom: Comparison of the effects of ibogaine and 18-MC (40 mg/kg, ip, 19 h earlier) on acute cocaine-induced increases in extracellular levels of dopamine in the NAC. Each data point represents the mean percent of baseline ($\pm$ SEM) of at least 6 rats. Dotted lines represent the mean baseline levels in each experiment. Asterisks indicate significant differences ($p < 0.05$) from baseline.

sites, sodium channels, and the serotonin transporter. In functional assays, ibogaine behaves as a noncompetitive antagonist at nicotinic receptors, possibly acting as an open channel blocker.^{49,50} 18-MC has low micromolar affinities at all three opioid receptors (κ , μ , and δ) and at the 5-HT₃ receptor, but no affinity at NMDA receptors or the serotonin transporter.²² The affinities for both ibogaine and 18-MC are in the low micromolar range and therefore are not likely to mediate either their “therapeutic” or motor effects lasting 24–48 hours. It is possible, however, that some of the differences in binding profiles between ibogaine and 18-MC may account for a potentially higher therapeutic index for 18-MC. Ibogaine’s affinity at muscarinic (M1 and M2) receptors and at sodium channels is 2–3 times greater than that of 18-MC and may be responsible for ibogaine-induced bradycardia. Ibogaine binds with a 30-fold higher affinity to sigma-2 sites, compared to 18-MC, and studies have linked ibogaine’s actions at sigma-2 sites to its neurotoxicity.⁵¹ In addition, the possibility exists that the hallucinogenic effect of ibogaine is mediated by its actions on serotonin release, an effect not observed with 18-MC.⁴⁷ Preliminary data from this laboratory suggest that both 18-MC and ibogaine might have nanomolar affinities for nicotinic channels, an action that could indeed contribute to their prolonged anti-addictive effects.

PHARMACOKINETICS AND TOXICITY

Plasma Half-life and Tissue Distribution

Using gas chromatography–mass spectrometry (GCMS), plasma and tissue levels of both ibogaine and 18-MC have been determined.^{8,20} Both compounds have a short initial half-life (approximately 5–10 minutes). In both cases, the data fit a two-compartmental model and the terminal half-lives of ibogaine and 18-MC are slightly over 100 minutes.²²

Consistent with the two-compartmental model fit for their elimination, both ibogaine (ip) and 18-MC (ip and po) are highly sequestered in fat.^{8,20} However, in absolute terms, the fat levels of either ibogaine or 18-MC account for only a small fraction of the administered dose (approximately 10%), suggesting that both compounds are subject to rapid metabolism, possibly a substantial first-pass effect. Indeed, one active metabolite of ibogaine, noribogaine, has been well characterized both *in vivo* (e.g., see references 52 and 53) and *in vitro* (e.g., see references 54 and 55). However, preliminary data from our laboratory suggest that the terminal half-life of noribogaine is approximately equal to that of ibogaine. Recent work in our laboratory indicates that 18-MC may also have metabolites that, when isolated and purified, may contribute to the protracted behavioral effects of this compound.

Neurotoxicity

Unlike ibogaine, which induces whole body tremors at moderate doses (20–40 mg/kg) and Purkinje cell loss in the cerebellum at high doses (≥ 100 mg/kg),^{14–16} 18-MC (40 mg/kg) is nontremorigenic as assessed by visual observations and videotape recordings of rats.¹⁴ Consistent with its low affinity for sigma-2 sites, even multiple, high-dose (100 mg/kg) injections of 18-MC fail to produce neurotoxic effects on cerebellar Purkinje cells.¹⁸ Thus, unlike ibogaine, 18-MC does not appear to be neurotoxic.

Cardiovascular Studies

Preliminary studies in our laboratory with awake and freely moving rats demonstrated that ibogaine produces no effects on heart rate or blood pressure when administered at 40 mg/kg, ip; however, at higher doses (100 and 200 mg/kg, ip), ibogaine dose-dependently decreases heart rate, without altering blood pressure. This finding is consistent with anecdotal reports in humans that ibogaine can slow heart rate. In contrast, 18-MC, when administered at 200 mg/kg, has no effect on either heart rate or blood pressure.²⁰ Thus, in terms of cardiovascular side effects, 18-MC has a higher margin of safety than ibogaine.

DISCUSSION AND CONCLUSIONS

Results from animal studies demonstrate that 18-MC shares all the putative anti-addictive effects of ibogaine, but lacks the neurological and cardiovascular toxicity.

The acute effects of 18-MC on drug self-administration are also more selective than ibogaine in that ibogaine, but not 18-MC, reduces responding for nondrug reinforcers (food and water). Earlier work with ibogaine²⁹ and more recent work with 18-MC⁵⁶ indicate that neither ibogaine nor 18-MC simply shifts the dose-response function for drug self-administration to the left or the right. At least in the case of morphine, both compounds shift the dose-response curve for self-administration downward, lowering the maximal response to morphine. This indicates that ibogaine and 18-MC reduce the reinforcing efficacy of morphine. The reduction in reinforcing efficacy of morphine may be attributed to a blockade of the psychomotor-activating properties of morphine in morphine-experienced animals; consistent with this interpretation, 18-MC blocks the expression of sensitization of locomotor behavior following chronic morphine treatment (FIGURE 5) and previous studies demonstrated that ibogaine produces a greater reduction in morphine-induced locomotor stimulation in morphine-experienced rats.³⁵ Studies of stimulant-induced motor behavior demonstrate that both ibogaine and 18-MC enhance the sensitivity of animals to the locomotor and stereotypic effects of cocaine and the amphetamines.^{31,32,57} As higher doses of stimulant drugs can produce aversive side effects in humans,⁹ it has been proposed that both ibogaine and 18-MC may decrease drug self-administration of stimulants in animals by potentiating the aversive effects of these drugs.^{28,31,32}

The precise mechanisms of the antiaddictive action of ibogaine and 18-MC are still unknown. Both of these compounds have relatively similar affinities for 5-HT₃ receptors, the manipulation of which alters amphetamine-induced euphoria in humans⁵⁸ and cocaine-induced locomotion, cocaine discrimination, alcohol consumption, and morphine withdrawal signs in rodents.^{59–63} These compounds also have similar affinities for μ and κ opioid receptors, and other data^{64–66} indicate that μ antagonists and κ agonists can modulate the self-administration of cocaine and/or morphine. However, the protracted antiaddictive effects of ibogaine and 18-MC are hard to reconcile with their micromolar range affinities for these receptors. In addition, both ibogaine^{10,11} and 18-MC²¹ attenuate naltrexone-precipitated withdrawal symptoms in morphine-dependent rats, findings that are inconsistent with μ antagonist activity; both ibogaine⁶⁷ and 18-MC²⁰ have little or no analgesic activity, findings that are inconsistent with μ agonist activity. The short-half life of 18-MC indicates that, like ibogaine, the pharmacological action of these compounds is attributable to one or more active metabolites. As both ibogaine and 18-MC are deposited in fat, this raises the possibility that slow release of these compounds, or perhaps their metabolites, may contribute, in part, to some of their protracted effects.

The issue of whether or not 18-MC shares ibogaine's hallucinogenic properties awaits the initiation of clinical trials; however, given that 18-MC does not raise extracellular levels of serotonin⁴⁷ or bind to the serotonin transporter (TABLE 2), it is predicted that 18-MC will lack hallucinogenic activity. In terms of the other side effects of ibogaine, work to date indicates that 18-MC is less toxic than ibogaine with respect to both neurological and cardiovascular effects.

In conclusion, 18-MC is a novel *iboga* alkaloid congener, derived from the putative antiaddictive agent, ibogaine, that may potentially serve as a safe and effective treatment for multiple forms of drug abuse. Further investigation of the *in vivo* and *in vitro* mechanisms of both ibogaine and 18-MC should assist in the elucidation of the psychobiological basis of addiction and contribute to the development of new agents with improved antiaddictive efficacy.

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